REMARKS

The Invention

The invention is based on the identification of T-cell epitopes in Japanese pollen allergen molecules. Thus, the invention features peptides containing the T-cell epitopes, compositions containing the peptides that are useful in immunotherapy of patients with spring tree pollinosis, analogs of the peptides, and methods of treatment and diagnosis using the peptides.

Status of the claims

After entry of the amendments made herein, claims 1, 2, 5, 7, 11, 13, 14, 17, and 20-47 will be pending, and claims 1, 5, 29-35, 38, and 39-47 will be under consideration in this application, claims 2, 7, 11, 13, 14, 17, 20-28, 36 and 37 having been withdrawn as allegedly being drawn to separate inventions and claim 47 having been added herein. New claim 47 is supported by the specification, e.g., at page 20, line 17, to page 21, line 1, and adds no new matter.

35 U.S.C. § 112, first paragraph, rejections

(a) Claims 41-46 stand rejected on the grounds that the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. In addition, claims 43-46 stand rejected as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

With respect to claims 41 and 42, the Examiner alleges that the instant specification does not teach how to "prevent" pollinosis by administering a peptide of the present invention. The Examiner finds there to be insufficient *in vivo* working examples demonstrating that the claimed peptides can be used to prevent pollinosis. The Examiner further alleges that the specification fails to provide guidance as to the process for selecting asymptomatic individuals and means for predicting which individuals would have developed allergy and which would not have.

With respect to claims 41 and 42, Applicants submit that individuals "susceptible to pollinosis" do not include asymptomatic individuals. The term refers to individuals showing symptoms as well individuals who exhibit symptoms during the pollen-scattering season. Symptoms occur in pollinosis only during this limited period. Administration of anti-allergic agents prior to the pollen-scattering season is well-recognized in the art as an effective modality for preventing pollinosis. Thus, one skilled in the art would believe it likely, given the teachings of the instant application, that administration of one (or more) epitope peptides of the present invention to an individual with pollen allergy prior to the pollen-scattering season would prevent pollinosis symptoms during the pollen-scattering season in that individual. In order to make this concept even clearer, Applicants have amended claims 41 and 42 by replacing the term "an individual susceptible to said pollinosis" with "a patient that has pollinosis in the pollen-scattering season".

With respect to claims 43 and 44, the Examiner asserts that the specification does not teach a method of diagnosing pollinosis by determining *any* lymphocyte response. Similarly, the Examiner asserts that there is insufficient written description regarding *any* responsiveness of all lymphocytes as an indication of an individual's susceptibility to pollinosis. According to the Examiner, the specification discloses only T lymphocyte proliferation as correlating to one's susceptibility to pollinosis; moreover, the term "responsiveness" broadly encompasses inhibitory and stimulatory response which are mutually exclusive.

Contrary to the Examiner's assertions, the instant specification does describe a variety of T cell "responses" as being indicative of the presence of stimulating T cell epitopes. For example, peptides found to induce T cell responses such as proliferation, secretion of lymphokines, and/or T cell anergy (i.e., non-responsiveness) are defined in the instant specification as having T cell stimulating activity; T cell epitope peptides that possess any such T cell-stimulating activity thus contain at least one T-cell epitope (see, for example, page 7, line 25, to page 8, line 4, and page 8, lines 21-26). In addition, with respect to the Examiner's statement that peptides can activate either inhibitory or stimulatory responses, in view of the definitions in the specification referred to above, it is clear that the term "stimulation of

lymphocytes", in the context of the instant application, covers both inhibitory and stimulating (or activating) responses of T cells. Thus, in the interest of further clarity, Applicants have amended the claims to refer to a step of "detecting *stimulation* of the lymphocytes in response to the peptide as an indication that the individual is susceptible to pollinosis caused by Japanese cypress pollen allergens or by tree pollen allergens that are immunologically cross-reactive with Japanese cypress pollen allergens." Such specific T cell responses, encompassing both stimulation of proliferation and stimulation of lymphokine production, are, as indicated above, both adequately described and enabled by the instant specification.

With respect to claims 45 and 46, the Examiner, citing Stryer *et al.*, Ngo *et al.* and Fasler *et al.* as evidence, asserts that there is insufficient guidance in the specification as to which amino acids within the peptide can tolerate change so as to enable on skilled in the art to make and use the claimed invention in accordance with the scope of the claims. The Examiner further asserts that there is insufficient written description in the specification regarding the structure associated with the function of *any* analog peptide or modified peptide without the amino acid sequence.

On the issue of enablement, it is important to note that the test for enablement is not whether one can "predict every species of compound falling within a claimed genus". Rather, the test is whether one of ordinary skill in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See M.P.E.P. 2164.01 and United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1233 (Fed.Cir. 1988). For an Examiner to sustain a rejection on the grounds of enablement, he or she must provide *evidence* that the claimed method could not be practiced *without undue experimentation*.

The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In fact, there are many factors to be considered when determining whether a specification is enabling and whether any necessary experimentation is

"undue". They include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention.

The Examiner is reminded that there is no statutory requirement for working examples. In re Borkowski, 154 U.S.P.Q. 643 (C.C.P.A. 1970), In re Rainer, 146 U.S.P.Q. 218 (C.C.P.A. 1965). Since the peptides of the instant invention exhibit T-cell stimulating activity, one of ordinary skill in the art would expect them to protect a person susceptible to pollinosis from exhibiting the symptoms of pollinosis, *i.e.*, to prevent pollinosis in that patient. In the instant invention, the claimed T cell epitope peptides are short peptides with an average length of about 15 amino acids that bind in the form of unfolded linear chains to a groove in MHC class II molecules. Accordingly, the number of substitutions that meet the structural and functional requirements of the instant claims is not indefinite but imminently calculable. Stryer *et al.*, Ngo *et al.* and Fasler *et al.*, cited by the Examiner, all disclose that *the tertiary structure* of proteins may be changed by amino acid substitution. Thus, the teachings of these references cannot be applied to linear short peptides of the instant invention. As discussed in the present specification (*e.g.*, at page 12), amino acid residues that participate in interactions with the T cell receptor can readily be determined using known methods (*e.g.*, by measuring the change in T cell stimulating activity that occurs upon substitution). Any amino acid residue found to be essential for interaction with the T cell receptor can then be substituted with another amino acid residue so as to identify residues that specifically control the T cell stimulating activity and hence suppress, for example, allergic inflammation. The effect of such substitutions on, for example, T cell responsiveness or pattern of lymphokine production, can be measured using methods entirely familiar to those in the art. Similarly, as described in the instant specification (*e.g.*, at pages 12-13), amino acid residues essential for interaction with HLA class II molecules can also be routinely identified and modified using conventional and well-known techniques. Specifically, the HLA class II molecule-binding motif of HLA class II molecule-binding peptides consists of three to five amino acid residues separated from each other by one or two essentially irrelevant

amino acid residues. When these motif residues consist of several kinds of specified amino acids, the peptide binds to the HLA class II molecule. Thus, using merely routine experimentation, one could readily identify potential residues for substitution and sequentially modify residues to arrive at a panel of analog peptides suitable for further testing.

Accordingly, one of ordinary skill in the art could not only readily synthesize panels of candidate analog peptides, using conventional tools such as site-specific mutagenesis and the like, but could also readily determine which of the candidate analog peptides function in the manner specified by amended claim 45 (see below). That is, one could also readily determine which of the analog peptides have T cell stimulating activity equivalent to that of the parent wild-type peptide. Methods for measuring relative levels of T cell stimulatory activity are well known in the art and include the protocol set forth in Example 5 (pages 19-20) of the instant specification.

Also with respect to enablement, Applicants have amended claim 45 to specify that the analog peptides of the invention differ from respective wild-type parent peptides by only one amino acid. Although, as indicated above, the amount of experimentation required to practice an invention is not dispositive with respect to enablement of the invention, this amendment greatly decreases the amount of experimentation that would be required to make an analog peptide within the scope of claim 45.

Thus, analog peptides that function as T cell epitopes of Japanese cypress pollen allergen Cha o 1 are amply enabled by the instant specification.

As noted above, there is no statutory requirement for working examples. In re Borkowski, supra, In re Rainer, supra. Since the analog peptides claimed are required to retain T cell stimulating activity equivalent to that of a wild-type peptide, one of ordinary skill in the art would expect them to be effective in the immunotherapy of pollinosis.

Compliance with the written description requirement is determined by asking the question: "Does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed?" The issue of whether or not the written description requirement is met is factual and depends on the nature of the invention and the amount of

knowledge imparted to those skilled in the art by the disclosure. Furthermore, it is well accepted that a specification may, within the meaning of 35 U.S.C. 112, first paragraph, contain an adequate written description of a broadly claimed invention without describing all species encompassed by the claims. The law does not require that the specification describe the exact details for preparing each and every species within the genus described. In fact, even if the Examiner considers the subject matter of the claims to be broader than that disclosed in the original specification, the written description requirement may be satisfied if the broader concept would naturally occur to one skilled in the art upon reading the earlier specification. Overbreadth has been discredited as a basis for determining sufficiency of a specification.

Contrary to the Examiner's allegation, the present invention is not directed simply to *any* analog peptides but to a specific subset of analog peptides in which specific amino acid residues are substituted (*i.e.*, those that mediate interaction with a T cell receptor or a major histocompatibility complex (MHC) class II molecule) and that retain the T cell stimulating activity of the wild-type peptide (*i.e.*, function as T cell epitopes of Cha o 1). The fact that Applicants do not provide a list of specific residues "tolerant to change" or examples of specific analog peptides is not dispositive on the issue of written description. As discussed above, the number of functioning analog peptides within the scope of the claims is not indefinite but imminently calculable, especially in view of the above-described amendment to claim 45. Moreover, as discussed above, one of ordinary skill in the art would readily recognize that certain amino acid substitutions can be made to the sequences without eliminating function and that the resulting analogs could be made and tested using conventional techniques and routine experimentation. Accordingly, one of ordinary skill in the art would be appraised of the "analog peptides" covered by the instant claims from a reading of the instant specification. Thus, the claims to analog peptides that function as T cell epitopes of Japanese cypress pollen allergen Cha o 1 are sufficiently described by the instant specification.

(b) Claim 40 stands rejected as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, has possession of the claimed invention.

The Examiner asserts that the term "consisting essentially of" in claim 40 does not find support in the specification or claims as originally filed. While not agreeing with this assertion, in order to expedite prosecution of the instant application, Applicants have amended claim 40 by replacing "consisting essentially of" with "comprising".

In light of the above considerations, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

35 U.S.C. § 112, second paragraph, rejection

Claims 43-46 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

With respect to the comments on page 6, lines 9-10 of the Office Action, in order to expedite prosecution of the instant application, Applicants have amended claims 43 and 44 to refer to a "method of diagnosing pollinosis".

In regard to the comments on page 6, lines 10-13, of the Office Action, Applicants point out that, because a term is broad, does not necessarily mean that it is indefinite. Nevertheless, the above-described amendments to claims 43 and 44 clearly overcome any possible indefiniteness in the claim.

With respect to the comments on page 6, lines 15-18, of the Office Action, Applicants have amended claim 45 to define the analog peptide using language similar to that used to define the peptide fragments of claim 1, namely, as "having T-cell stimulating activity equivalent to that of the wild-type peptide". This language was previously deemed acceptable by the Examiner (see the Amendment and Response of February 13, 2003).

Regarding the comment on page 6, lines 19-20, of the Office Action, Applicants have amended claim 46 to specify an "analog peptide" rather than a "modified peptide".

Applicants respectfully submit that the above amendments render the rejections under 35 U.S.C. § 112, second paragraph, moot.

35 U.S.C. §102(b) rejection

Claims 45-46 stand rejected as allegedly being anticipated by WO94/01560.

The Examiner asserts that the cited reference teaches an analog peptide, CJI-17, which is an analog peptide of the wild-type peptide with SEQ ID NO: 9, has more than one amino acid substitution, and stimulates T cell proliferation.

While not agreeing that the cited reference anticipates claims 45 and 46, in order to expedite prosecution of the instant application, Applicants have: (a) amended claim 45 to specify the substitution of only one amino acid residue; and (b) have put claim 45 in independent form, incorporating all the limitations of claim 1, except Peptide #1-5 (SEQ ID NO: 7), Peptide #1-22 (SEQ ID NO: 24), and Peptide #1-25 (SEQ ID NO: 27) as wild-type peptides.

In light of the above considerations, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that the claims under consideration patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action and permit the claims under consideration to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a Petition for an Extension of Time with the required fee. Please charge any other fees or make any credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14883-024001.

Respectfully submitted,

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